The Cardiovascular Aspects of Marfan's Syndrome: A Heritable Disorder of Connective Tissue

By Victor A. McKusick, M.D.

Clinically, Marfan's disease behaves as an atrophy of some connective tissue element. Cardiovascular manifestations result from defective aortic media, defective valve cusps, interatrial communication, and pectus excavatum. The defect of the aortic media manifests itself by dissecting aneurysm, diffuse aneurysm of the ascending aorta or a combination. Subacute bacterial endocarditis in a patient with Marfan's disease is described. Interatrial septal defect is less frequent than previously believed. Cardiac symptoms in severe pectus excavatum must be evaluated in light of possible Marfan's disease. Fifty families in which at least one bona fide instance of Marfan's disease has occurred were collected.

As part of a study of hereditable disorders of connective tissue, the total genetic, clinical and pathological picture of Marfan's disease has been analyzed in 50 kinships in which at least one bona fide instance of this condition has occurred. The total number of definitely affected persons is approximately 105; this figure cannot be stated more dogmatically since, as might be expected, borderline cases were encountered in a number of the families.

A majority of the families for this study was discovered by examination of all available instances of congenital subluxation of the lenses; study of the individual patients and of their relatives revealed stigmata of Marfan's disease in approximately 70 per cent of these. Other specialities, particularly pediatrics, orthopedics and endocrinology, provided leads on cases. The Medical Examiner,* who is likely to see those cases of Marfan's syndrome which end in sudden death, has been another significant source of cases. Cases of dissecting aneurysm of the aorta from this source and from hospital pathology files have been studied from the point of view of inherited connective tissue abnormality of the Marfan type. Finally, the families of all cases ever diagnosed as arachnodactyly or Marfan's syndrome at the Johns Hopkins Hospital have been traced when possible and studied. The occurrence of multiple cases in many of these families, e.g., 15 in one, nine in a second, has swelled the total.

Other factors of this study,† including the

*The writer is indebted to Dr. Russell S. Fisher for permission to use the files of the Medical Examiner's Office of the City of Baltimore.
†The genetic data support the view that a single mutant gene is responsible for all aspects of this complex syndrome. One would suspect that there is, in some element of connective tissue, a basic biochemical defect, having widespread repercussions and resulting in the varied manifestations of this syndrome. The precise defect is yet to be identified. However, in a situation such as this it is possible to

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genetic aspects, will be reported elsewhere. It is the purpose here to record the experience with abnormalities in the cardiovascular system. Such abnormalities, of at least mild degree, were detected in 46 individuals with possible abnormalities in 11 others.

It is convenient to discuss the cardiovascular aspects of Marfan's syndrome and to classify the cases according to the following outline:

I. Aorta:
1. Dilatation of aortic ring.
2. Dilatation of ascending aorta.
3. Dissecting aneurysm.
4. Combinations of 1, 2 and 3.
5. Coarctation.

II. Pulmonary Artery:
1. Dilatation (including some cases of so-called "congenital idiopathic dilatation").
2. Dissecting aneurysm.
3. Microscopic alterations of media.

construct a "pedigree of causes" as is given in figure 1. The chart reviews the components of this syndrome. Special attention is directed to those manifestations indicated by interrupted lines: in the skeletal system, spina bifida occulta and hemivertebrae; in the heart, interatrial septal defect and coarctation of the aorta; in the eye, coloboma of the lens and microphakia. In the present state of our knowledge these congenital anomalies of the more conventional type are difficult to explain on the basis of a unitary defect of connective tissue unless one assumes that the presence of this defect during embryogenesis produces an abnormal setting in which these particular anomalies occur with increased incidence. If this is true, these less frequent manifestations indicated by the interrupted lines may be considered secondary ones.
III. Septal Defects:
   1. Atrial.
   2. Tetralogy of Fallot.
IV. Valvular Abnormalities:
   1. Stretching and saculation of the aortic cusps.
   2. Other gross and microscopic changes.
V. Dysrhythmias and conduction defects.
VI. Pectus excavatum.

Aortic Lesions

A number of the early autopsies in cases of Marfan's syndrome, all infants and children, revealed patency of the interatrial septum. "Congenital heart disease" in general and this defect specifically came to be considered the cardiovascular hallmark of this disorder. As adult patients were recognized and studied, it became clear that a structural abnormality in the great vessels leads to manifestations which are both more frequent and clinically more significant. Although a very few references* to aortic abnormalities in association with arachnodactyly are buried in the earlier literature, the first definitive description of the two complications to which the aortic defect predisposes, diffuse dilation of the aorta2 and dissecting aneurysm of the aorta3 appeared in 1943.

* One such instance is the case of a six year old child with aneurysm of the ascending aorta which ruptured into the pericardium, reported by Bronson and Sutherland in 1918.46 "The unusual shape of his head and ears and the looseness of his joints attracted attention early in infancy." Inguinal hernia was repaired surgically at the age of two years and a left diaphragmatic hernia was discovered by x-ray examination. He was always undernourished but was sensitive and mentally advanced for his age with a quaint way of expressing himself and "a sense of humor of his own". The forehead was high and full, the palate highly arched. The ears were large without the normal folds of the pinnae. The joints were lax, the limbs flail-like and the elbows showed definite subluxation. There was lordosis and pigeon-breast with an increased prominence of the right side of the chest which showed better expansion. A pulsating mass was discernible to the right of the sternum. Although no diastolic murmur was mentioned, the left ventricle was hypertrophied at autopsy. There was also partial coarctation proximal to the

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The predominant involvement of the base of the aorta or most of the ascending aorta (in progressively lesser degree as one passes away from the heart, usually with rather sharp stopping of the alterations at the mouth of the innominate artery) is by no means inconsistent with this disease, it being a generalized disorder of some connective tissue element such

left subclavian artery. It is impossible to imagine a better description of the condition under discussion here. The authors also presented a detailed review of reports previous to that time; many of these cases also are reasonably clear instances of Marfan syndrome.
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The ascending aorta is subjected to pressures which are maximal for the arterial tree. As the pulse wave moves out in the vascular tree, the effective size of the elastic chamber into which the ventricle is ejecting is constantly increasing. The first sharp increase in the volume of this reservoir occurs at the innominate artery. There can be little doubt that the preinnominate ascending aorta is under maximal arterial stress and that this fact is, to a considerable extent, responsible for the localization of predominant involvement in both syphilis and Marfan's disease. The observations of Reynolds that with physiological pulse pressures only the ascending aorta shows appreciable dilatation is probably pertinent in this connection.

Diffuse Aneurysm of the Ascending Aorta. When this particular abnormality occurs in Marfan's syndrome it is almost always limited to the ascending aorta, stopping abruptly just before the mouth of the innominate artery. (Clinically in case 3 of Thomas and co-workers the descending aorta was also involved.) That the aortic ring and adjacent intrapericardial portion of the aorta are first affected is clear from the clinical course and has been demonstrated pathologically in cases dying before full-blown changes had developed. This feature is of great clinical significance since frequently these patients have profound aortic regurgitation with little or no demonstrable aortic dilatation. Syphilis, rheumatism, or bacterial endocarditis is often suspected first; when these appear unlikely from collateral evidence and when, as is so often possible in all sorts of disorders, a history of trauma is elicited, traumatic rupture of a normal aortic cusp is postulated. Furthermore, a deceptive prominence of the pulmonic conus and main pulmonary artery may result from displacement of these structures by the dilated intrapericardial portion of the ascending aorta. This radiologic feature was very striking in case 2 of Baer and associates. The pulmonary artery may, of course, be dilated as a result of intrinsic involvement of its media. Whatever the cause, the prominence of the pulmonary artery together with the Austin Flint murmur of aortic regurgitation leads frequently to the false diagnosis of rheumatic heart disease with combined aortic and mitral lesions. Such was the case in the patient, aged 49 years, whose chest x-ray is presented in figure 2, in spite of the fact that he was 6 feet 3½ inches tall, he had a spinal and thoracic deformity and had had ectopic lenses removed 10 and 13 years previously.

The aortic cusps, which probably participate in the same connective tissue defect, become enormously sacculated. Their defect may contribute to the aortic regurgitation. The stretching of the aortic cusps may proceed to the point that breaks with fenestration of the valve leaflets result. At times the murmur of aortic regurgitation may be exceedingly loud and audible at a distance from the chest.

It may have the musical "cooing" character commonly associated with rupture or eversion of an aortic cusp. Although, as mentioned above, traumatic rupture is frequently suspected, it is possible that such
rupture of the defective aortic cusps may occur with or without physical strain in a patient with Marfan's syndrome.

By examining and following patients with ectopia lentis and their families, I have discovered three individuals who appear to be at the very inception of their aortic regurgitation. Figure 3 A and B presents such a case (the father). The aorta is not evidently dilated. In two of these very early cases the second aortic sound has a tambour quality reminiscent of that in syphilitic aortitis.

A number of years after aortic regurgitation is first observed these patients are likely to develop angina pectoris and left ventricular failure. The prognosis thereafter is identical with that of severe aortic regurgitation of syphilitic origin. Most of the patients succumb within two years after the onset of significant symptoms. Granting the importance of other factors in the angina pectoris, one cannot help but wonder if one factor may not be the pronounced dragging of the large blood-laden aortic cusps on the coronary ostia. The coronary ostia become displaced to a higher position relative to the aortic commissures just as occurs in syphilitic aortitis.

Aortic dilatation with aortic regurgitation was the principal cardiovascular abnormality in at least 11 patients in this series. A boy was found to have the murmur of aortic regurgitation at the age of five years following a bout of pertussis and died at the age of 7 3/4 years. Another patient died at the age of 50 years, an aortic diastolic murmur having been first discovered 10 years before and bouts of left ventricular failure followed by right-sided failure having begun three years before. In a
reported case dilatation of the ascending aorta with aortic regurgitation and marked left ventricular hypertrophy resulted in the death of a ten month old infant, and in another death did not occur until the age of 55 years.

The patient presented in detail below is representative of the cases of aneurysmal aortic dilation in this series. An aortic diastolic murmur is known to have been present for at least nine years before death and seven years before the onset of left ventricular failure and angina pectoris. He lived 21 months after the onset of these symptoms. The correct diagnosis was not suspected until late because of inconspicuous dilatation of the aorta until the last year of life, failure to detect the ectopia lentis, and partial submersion of the characteristic habitus in the general pyknic build of the family from which the patient sprang. Earlier in the patient's course traumatic rupture of a normal aortic cusp was considered the probable diagnosis.

L. K. (J.H.H. 571745), a white man born in 1913, was first admitted to this hospital in May, 1951. On April 16, 1951, while riveting at an aircraft plant he noted the rather sudden onset of severe steady pain in his right chest radiating down the right arm. This disappeared in a few hours, and he was essentially asymptomatic thereafter, but was aware of profuse sweating particularly of the hands and feet.

Examination revealed that the blood pressure was 195/40/0. He was a slightly built man of average height. There was alternating external strabismus and the pupils were rather small but normally reactive. No other ocular abnormality was detected at that time. There were pronounced cardiac and peripheral signs of aortic regurgitation.

There was no history of rheumatic fever or syphilis and no laboratory or clinical evidence of syphilis or bacterial endocarditis. There was a story that in his work as a riveter the instrument which he held in front of his chest had, on several occasions, slipped, striking his chest forcefully. The possibility of traumatic rupture of an aortic cusp was considered most likely. In fact this was considered so likely by his physicians that with their assistance the patient succeeded in making a $4,000 settlement with his employer! The history of his having been previously turned down for insurance was not elicited.

The patient was virtually asymptomatic until September, 1951, when he began to have attacks heralded by very profuse sweating and consisting of pain under the lower sternum, severe palpitation, and coughing. Rapid eating and excitement would precipitate the attacks. They occurred most often about midnight.

The patient's second admission was in May, 1952. At that time Dr. F. W. Dick first noted that the patient had iridodonesis bilaterally and that the edge of ectopic lenses could be seen with the opthalmoscope. Since the age of 10 years the patient had worn glasses for myopia and bifocals since the age of 19 years. Examination revealed profuse sweating even in a cool room. The lid slits were wide and there was lid lag; these were interpreted as probably being related to the effort to accommodate. (The excessive sweating was probably that frequently seen with left ventricular failure.) The head was round and neck rather short. There was kyphosis without scoliosis. Muscular development was on the whole rather poor. The shoulders were rounded and scapulae moderately winged. His height was 5 feet 7 inches, fingertip-to-fingertip span 5 feet 11 inches. Pubic symphysis to heel dimension was 34 inches (over half his total height). There was syndactylyism of the second and third toes bilaterally. At this time there was a diastolic thrill at the right border of the sternum and mediastinal dullness was increased to the right.

It was now very apparent that the patient had Marfan's syndrome. Superannuated dissecting aneurysm of the aorta was considered likely.

The remainder of the patient's life was characterized by severe attacks of sweating, anginal pain, and orthopnea. At no time were there signs of right-sided failure. Comparison of early and late films are presented in figures 4A, B, C, D. The patient died Jan. 23, 1953.

At autopsy (424300) his height was determined to be 5 feet 6 inches. (There is a discrepancy among the various reported measurements.) The kyphosis was again described. The significant findings were limited to the heart which weighed 980 Gm. (fig. 4C). The increased weight was almost entirely the result of very marked left ventricular hypertrophy. The ascending aorta was the site of pronounced fusiform dilatation. The aortic valve ring was dilated to about four times the normal circumference. The sinuses of Valsalva were greatly dilated and the aortic valve cusps themselves were relatively enormous baggy structures. The aortic dilatation stopped at the mouth of the innominate artery. Beyond the mouth of the left subclavian the aorta narrowed sharply in a typical, although only partial (about 40 per cent), stenosis of the isthmus.

Microscopic sections of the aorta (see figure 4D) revealed replacement of most of the media by scar tissue. There were some areas of cystic medial degeneration. Elastic tissue stains revealed marked
disruption, fragmentation and sparcity of elastic fibers.

After the death of the patient, an investigation revealed, in the records of an insurance company, information that the patient was turned down for insurance in 1944 because of aortic regurgitation. Therefore an aortic diastolic murmur had been present for at least nine years before death and for
several years before symptoms of significance. It should also be noted that he had had varicose veins which required surgical treatment.

Comments. A point of great diagnostic interest and importance is illustrated by the x-ray films shown in figure 4, namely the fact that the aorta was not conspicuously dilated at the time the patient was first seen, in spite of the presence of striking aortic regurgitation. A possible useful point may be in the finding at fluoroscopy at the time of the first admission that "the lower right border of the heart in the region of the right atrium showed a marked increase in amplitude of pulsation. The pulmonary artery segment on the left side of the heart also pulsed vigorously, although the vascular markings of the lung were if anything decreased." As pointed out above, in some of these cases the outflow tract of the right ventricle and base of the pulmonary artery are evidently displaced forward and to the left (by the dilatation of the base of the aorta), simulating enlargement of these structures. On the other side the intrapericardial portion of the aorta may be responsible for displacement and active pulsations in the right atrium.

A feature of equal diagnostic significance and of considerable genetic interest is the relative submersion of the full-blown skeletal manifestations when the Marfan mutation occurred in this pyknic stock. When first seen the patient did not impress anyone as being beyond the normal range as to habitus. Discovery of ectopic lenses resulted in the observer being more impressed with the habitus. Comparison with his brothers and sisters would likewise have impressed the physician with the patient's abnormality. Other members of the family were about 5 feet 3 inches tall and were very heavily muscled with short powerful extremities and stubby fingers. The moral to the diagnostican is obvious. Although extensive studies of the families were not undertaken, several cases in the literature probably illustrate this same phenomenon.8

This case bears many resemblances to case 3 of Tung and Liebow.9 The type of aortic involvement which they illustrate is almost identical to that in figure 4C. Their patient, who died of aortic insufficiency at age 42, had had two herniorrhaphies and had varicose veins. Although the authors state that "no suggestion of arachnodactyly nor of any other external sign of Marfan's syndrome (was) recorded by any of several senior physicians who were concerned with the care of this man," it must be noted that he died in 1932 which was before a single case of this syndrome had been reported in the internal medical literature of this country and over 10 years before the association of aortic dilatation and arachnodactyly was first clearly described.2

Dissecting Aneurysm. The same lesion which may result in diffuse dilatation may be the basis for dissecting aneurysm of the aorta. In fact the two complications occasionally coexist (see figure 3 in ref. 42 and figure 2 in ref. 54). This is, then, another mechanism for an association of the murmur of aortic regurgitation with dissecting aneurysm.16 That the lesions are not necessarily limited to the ascending aorta is indicated by cases of arachnodactyly and dissecting aneurysm in which dissection and cystic changes were observed in the abdominal aorta.11, 12 In case K. B. reported below, two dissections were present in the aorta, one proximal and one distal to a partial coarctation. In a patient described by Weve48 in 1932, laparotomy revealed aneurysm of the aorta extending from the diaphragm into the pelvis. Sudden death on the basis of dissecting aneurysm with rupture into the pericardial sac or pleural cavity was demonstrated to have occurred in several patients of this series and from the history is suspected to have occurred in several others.

To my knowledge the oldest patient succumbing to this complication of Marfan's syndrome was 52 years old;12 a 48 year old patient dying of dissecting aneurysm on this basis was discovered in this series.

At least one patient in this series survived the acute dissection for about two years, demonstrating aortic regurgitation which from autopsy evidence appeared to have been due principally to distortion of the aortic ring by
the intramural hematoma. In one case described as "chronic dissecting aneurysm of the aorta resembling chronic rheumatic heart disease" historical and physical features typical of Marfan's disease are enumerated although the existence of a generalized connective tissue abnormality was apparently not appreciated by the authors. In still another case reported as "chronic dissecting aneurysm simulating syphilitic cardiovascular disease," Marfan's syndrome mimicked the "Great Mimic." The occurrence of aortic regurgitation with dissecting aneurysm is well recognized in this country since Resnick and Keefer's description in 1925. Hamman's explanation (distortion of the aortic ring by the intramural hematoma) is the usually accepted one.

A combination of terminal dissection of the aorta with previous dilatation of the ascending aorta occurred in several of the patients in this series including the two Medical Examiner's cases who are described briefly below:

1. R. L. L., a 37 year old unmarried white man, dropped dead on March 19, 1953, while being interviewed for employment. Necropsy revealed dilatation of the ascending aorta and dissection of the aorta with rupture into the pericardial sac. From the application form he had just filled out for employment and from conversations with his parents in a distant state, the following facts were pieced together. He was 74\(^\frac{1}{2}\) inches tall and weighed 220 pounds. He had always been stout. "A cartilage" projected on one side of the front of his chest. He had flat feet and knock-knees for which he was turned down for the Army but subsequently was taken into the Air Corps where he served four years and attained master sergeant rating. His knees gave him much trouble and required operation while he was in the service. For several years before his death his family noted a collapsing type of active pulsation in the neck. He was dyspeptic on climbing stairs but this was attributed to obesity. He lacked his usual energy. After his death digitalis was found on his person and it was found that unknown to his parents with whom he lived he had been under medical care for some time. This appears to have been a sporadic case inasmuch as a sister, the parents, grandparents, aunts, and uncles, appear to be unaffected by anything resembling Marfan's disease.

2. W. W., a 24 year old white boy, died suddenly on July 8, 1944, following a high dive. Necropsy revealed dilatation of the ascending aorta and dissecting aneurysm with rupture into the pericardial sac. This patient was 73\(^\frac{1}{2}\) inches tall and is described by his father as having been "well built." He was an active wrestler, ice skater, swimmer. He was turned down by the Selective Service examiners about 18 months before his death because of aortic regurgitation. He was advised not to dive. No eye abnormality was known and he had had no trouble with hernia or flat feet. He was employed in war industry in Baltimore at the time of his death.

The parents and two siblings are said to be well although there has been no opportunity to examine these individuals who live in another part of the country. A paternal uncle, 75 inches tall, died of "leakage of the heart" at the age of 60 years. He had, however, had rheumatism in younger years.

Other Aortic Abnormalities. Coarctation of mild degree, and of the adult type, was present in patient L. K. above and patient K. B. below. It has been previously described in patients with Marfan's syndrome. Two patients had patent ductus arteriosus and this, too, has been seen before. As mentioned in the footnote on page 2, these may be considered secondary manifestations of this condition. It is doubtful whether there has ever been a case of Marfan's syndrome with coarctation severe enough to be of clinical significance. (One patient in our group has hypertension and a small left radial pulse but no discrepancy in arm and leg pressures.) However, it is probably wise to be on the lookout for stigmata of Marfan's syndrome whenever either coarctation or patent ductus is encountered.

Whitfield, Arnott and Stafford described a case of simple hypoplasia of the aorta with Marfan's syndrome. They suggested that the increased resistance produced by the reduced aortic diameter might have been at least partially responsible for the cardiac hypertrophy in this case. Since hypoplasia of the aorta is a questionable explanation for symptoms or signs under any circumstances, the interpretation of these authors is doubtful. In at least one reported case, bacterial endocarditis was thought to be present, producing the clinical picture of subacute bacterial endocarditis. The site of infection was probably the first part of the descending aorta.
PULMONARY ARTERY LESIONS

Baer, Taussig and Oppenheimer\(^2\) described the same lesions in the pulmonary artery as occurred in the aorta of their two patients. However, these lesions were not sufficiently pronounced to have been of functional significance. Tung and Liebow\(^9\) have described the case of an infant in which the pulmonary arterial abnormality was of real clinical significance, and also that of an adult with a clinical picture which would justify the label of "idiopathic congenital dilatation" of the pulmonary artery. We have seen cases of both types and presented below is an example of the first. Anderson and Pratt-Thomas\(^37\) have recently reported another case in which involvement of the pulmonary artery dominated the clinical picture. In this patient rupture of the pulmonary artery into the pericardial sac occurred. In retrospect, surveys of the literature reveal cases which, from ancillary information, were almost certainly cases of aneurysm of the pulmonary artery on this basis.\(^44\)

"Idiopathic congenital dilatation" of the pulmonary artery\(^18\) is almost certainly not a homogeneous group. In some of the cases there is hypoplasia of the aorta. It has generally been considered a benign condition. If there is any reason to suspect that this is merely one component of Marfan's syndrome, the prognosis is, of course, quite different. Dissecting aneurysm occasionally occurs in the pulmonary artery on the basis of the medial abnormality of Marfan's disease.

In the infant described below, pulmonary artery involvement was of primary significance.

B. J. P. (H.L.H. A93754) was born Nov. 9, 1951. She weighed 6 pounds, 11 ounces, and was thought to be healthy. The mother had had no pregnancies in the 19 years between this one and that which occurred in 1933. The mother first learned of the child's heart murmur when the child was four months old. The child was never able to sit up or roll over by itself. When first seen at the age of six months, the following findings were recorded: The left side of the face was smaller than the right. Respirations were rapid (about 50 per minute). There was a pigeon breast deformity of the thorax. The pulse was regular at a rate of 150 per minute. Femoral pulses were full. The heart was enlarged beyond the left midclavicular line. A systolic thrill was palpable over the entire precordium but was maximum in the left midprecordium. A harsh systolic murmur had the same location. The liver edge was 1.5 cm below the right costal margin. There was no clubbing or cyanosis.

Fluoroscopy (see figure 5) revealed great cardiac enlargement to both left and right with globular shape. The right ventricle was definitely enlarged in the oblique views. The right lower lung field had a distinctly abnormal appearance. It lacked the usual lung markings and was unusually radiolucent. There was a question of atelectatic lung (\(\sim\) right middle lobe) at the right heart border. By electrocardiogram the P waves were broad and notched. The P-R interval was 0.16 second which is long considering the patient's age and heart rate of 150 per minute. Very large R waves in the leads from the left of the precordium suggested left ventricular hypertrophy. The hematocrit was 29.5 per cent with hypochromic, microcytic cell indices.

Late in May, 1952 the patient developed physical and x-ray signs of consolidation in the right upper lobe and became febrile. These signs were altered little by the administration of several different antibacterial agents. The heart was extremely overactive and shook the whole bed. Occasionally the murmur assumed a to-and-fro quality, especially at the lower left sternal border. The liver enlarged in size. Subsequently signs of consolidation of the entire right lung appeared. On July 31, 1952 it was noted that both lenses were misplaced mediad and

![FIG. 5. X-ray film of the chest in infant B. J. P. The pulmonary anomaly is evident as well as the pronounced cardiomegaly.](image)

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\(^3\) Tung, C. C., and Liebow, A. T.: Circulation, 1951, 2, 546.


that dilatation of the pupil with phenylephrine was only partially successful. Ophthalmologic consultants observed that the patient was extremely myopic with small lenses. In the last weeks of life there was an episode of hematuria related, perhaps, to sulfa-diazine therapy. Death occurred on July 10, 1952 when the patient was only 8 months old.

Autopsy (n 23761) revealed that the right lung was partially atelectatic. The left lung was normal. The pulmonary artery was larger in circumference than the aorta. The foramen ovale was imperfectly closed. All chambers of the heart showed hypertrophy of their walls and dilatation. The hypertrophy of the right atrium was particularly marked. Microscopically there were no lesions of the myocardium. However, the wall of the pulmonary artery and to a lesser extent that of the aorta showed typical changes of Marfan’s syndrome. The media contained vacuoles filled with metachromatically staining material and there was derangement and relative sparsity of elastic fibers. The wall of the pulmonary artery was thicker than that of the aorta. At the time of the gross examinations the bronchial tree was injected with radio-opaque material and radiograms were made. To the surprise of the prosector no abnormality was identified.

Comments. Obviously the most informative feature of this case is the advanced change in the pulmonary artery which undoubtedly resulted in pulmonary regurgitation and was a leading factor in the infant’s death at the age of only eight months. Ectopia lentium, myopia, microphakia, arachnodactyly, retardation of ability to sit or roll over complete the picture of Marfan’s syndrome.

This kinship illustrates one of the difficulties of genetic research in man. The illegitimacy of this infant and the presence of a legitimate wife made the utmost tact and resourcefulness necessary for collecting even these few data. The father of the infant is about 74 inches tall, has long hands and feet, and wears spectacles. Examination was not possible and no further pedigree information was obtained.

INTERATRIAL SEPTAL DEFECT

This lesion, the incidence of which in Marfan’s syndrome was exaggerated by earlier reports, is of real functional significance in occasional patients. The 12 year old girl described below is such a case. Almost all the cases are ones of patency of the foramen secundum (foramen ovale); the foramen primum type of patency has been described with certainty in only one autopsied case. Abnormality of the interatrial septum is possibly, like coarctation and patent ductus arteriosus, a secondary manifestation of the connective tissue defect.

One would expect that the combination of interatrial septal defect and inherent weakness of the pulmonary arterial wall might result in even more dilatation of the pulmonary artery than is usually seen with either lesion alone. This has not been demonstrated with certainty, however.

M. E. C. (J.H.H. A98174), born in 1940, was first referred to Dr. Helen B. Taussig in Nov., 1952, for investigation of her congenital heart defect and paroxysmal tachycardia. The father is 76 inches tall and very asthenic and has a spinal curvature and ectopia lentis but no evidence of cardiovascular abnormality.

In this case a heart murmur had been described before the age of two years. Except that she never gained weight well and could not keep up with the other children at play, the patient was relatively well until April, 1952, when she had a first attack of paroxysmal tachycardia lasting several hours. Two more attacks occurred, one in May and a second in Sept. 1952.

The patient was a tall, slender white girl of better than average intellect. She was 64 inches tall and weighed 79 pounds. She wore glasses for ectopia lentium, which had been discovered at the age of five years. The palate was high. The chest was long with convex scoliosis of the thoracic spine toward the right. The heart was not enlarged. However, a loud systolic murmur accompanied by a thrill was heard in the second and third intercostal spaces to the left of the sternum. The patient stood with rather marked pronation of the feet at the heels and moderate abduction. There was minimal genu valgum.

On fluoroscopy (see figure 6) the right atrium was seen to be enlarged and the main pulmonary artery was prominent and active. There was moderate hilar dance. The left atrium and the ventricles appeared to be normal in size. During the recording of the electrocardiogram short paroxysms of atrial tachycardia occurred. There was a higher degree of right axis deviation than would have been anticipated even at this age. Leads II and III showed changes in the ST-T complex interpreted as “right ventricular strain pattern.” The QRS complexes
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Fig. 6. Chest x-ray film in M. E. C., an instance of interatrial septal defect with Marfan's disease.

were notched in most leads. X-ray films revealed no structural abnormality of the vertebrae.

Surgical repair of the interatrial defect is probably worthwhile in this patient in spite of the presence of a generalized disorder of connective tissue which may express itself elsewhere in the cardiovascular system.

IS TETRALOGY OF FALLOT AN OCCASIONAL MANIFESTATION OF MARFAN'S SYNDROME?

We have encountered two patients with tetralogy of Fallot who have suggestive stigmata of Marfan's disease. In these cases the diagnosis of tetralogy is not in question although that of Marfan's disease is. Careless statements in the review literature notwithstanding, interventricular septal defect has never been established in a case of arachnodactyly. (In Cockayne's case ventricular septal defect was suggested on clinical grounds alone and even this evidence was scanty. There is a report of a possible tetralogy of Fallot with arachnodactyly.) The cases in this series had the Blalock-Taussig operation for tetralogy of Fallot and both had arachnodactyly but no ectopia lentis. In neither case were there stigmata of Marfan's syndrome in the other members of the family. One of the cases (J.H.H. 525256) had malformed pinnæ and spinal curvature from hemivertebra (fig. 7). The other patient (J.H.H. 482041) had cleft palate, pes planus, and talipes equinovarus.
Unexplained or poorly explained precordial systolic murmurs occur commonly in these patients. Redundancy of the chordae tendineae may be the basis of the murmur in some cases. The state of the chordae tendineae is often difficult to evaluate at necropsy because of the other gross abnormalities, especially ventricular enlargement. The thoracic deformity may be responsible for the systolic murmur in some instances.

Marginal thickening and nodular excrescences of the valve cusps, particularly of the mitral valve, occurred in a rather high proportion of autopsied cases. Tung and Liebow have described cystic changes in the mitral valve cusps with deposition of the same metachromatic coagulum as occurred in the aorta in the same case. On these valve changes bacterial endocarditis may apparently be grafted. Bacterial endocarditis under these circumstances was reported at least twice previously and occurred in the following pregnant patient with Marfan's syndrome:

M. E. R. (J.H.H. 176836), a colored female born in 1929, is a member of a family which has been known to this hospital for about 25 years and in which at least 10 cases of Marfan's syndrome (including this patient) have occurred. (The patient is individual III-11 in the pedigree presented in figure 8A.) The father of the patient, a well-documented instance of this syndrome, died of dissecting aneurysm of the aorta at the age of 43 years. Of four siblings of the patient with this disease three have signs consistent with interatrial septal defect.

The patient demonstrates bilateral ectopia lentis, severe myopia, pronounced dolichostenomelia, very poor muscular development, severe kyphoscoliosis, pes planus, and by x-ray films pulmonary emphysema with bleb formation. The patient is shown in figure 8B. She recalled nothing suggestive of acute rheumatic fever. Most of her life she had been subject to exertional dyspnea.

**Fig. 8.** A. Pedigree of the family of patient M. E. R. (III-11). Individual II-2 appears to have been the original mutant. B. Patient M. E. R. C. The combination of arachnodactyly and clubbing of the fingers relates to the Marfan's disease and subacute bacterial endocarditis from which the patient M. E. R. suffered. D. The mitral valve showing bacterial vegetation.
The patient became pregnant in early November 1953. After about four months there was increase in her life-long exertional dyspnea and the appearance of ankle edema and orthopnea which required two pillows. In early April 1954, there was onset of evening fever, night sweats, and aching joints, especially knees and ankles. Tender red spots appeared on the palms and soles.

Physical examination revealed as new findings petechiae, embolic nodes of the palms, splinter hemorrhages of the nail beds, and clubbed fingers. A loud harsh systolic murmur was audible over the entire precordium and the second pulmonic sound was accentuated.

Six blood cultures demonstrated a streptococcus viridans which was late in growing out and atypical in morphology due probably to streptomycin and penicillin which had been administered before admission to the Osler Medical Clinic. The patient's white blood cell count was 10 to 12,000 and hematocrit 26 per cent. Treatment with penicillin in large doses was instituted with seemingly successful results. Figure 8C reveals the unusual combination of arachnoidactyly and digital clubbing.

On the patient's twentieth day in the hospital premature labor began and an infant weighing 1700 Gm. was born. The infant, which demonstrated pronounced dolichostenomelia, lived only a very few minutes. Autopsy in the case of the infant revealed no cardiovascular lesion and the cause of death is not completely clear.

The patient died of uncontrollable heart failure about two weeks after delivery. Figure 8D shows the mitral valve with its vegetations in this case. No evidence of rheumatism was discovered. The media of the aorta was histologically normal.

Comment. It is, of course, impossible to be certain that the patient did not have a rheumatic lesion of the mitral valve on which her bacterial endocarditis was engrafted. It is by no means necessary that such is the case; Marfan's syndrome is adequate basis for all the developments in this case.

**Dysrhythmias and Conduction Defects**

Abnormalities of these types were encountered in a number of the patients of this series. Most of these abnormalities were probably functional consequences of the stresses and strains imposed by the other dysfunctions, principally aortic regurgitation and interatrial septal defect. Atrial fibrillation is known to have occurred at least six times. Paroxysmal atrial tachycardia occurred in the case of interatrial septal defect described above. Delayed atrioventricular conduction occurred in several cases with aortic regurgitation as did also left bundle branch block. Others have reported bundle branch block and partial atrioventricular block.

One patient, now 18 years old, with unequivocal ocular and skeletal signs of Marfan's disease has right bundle branch block as the only cardiovascular abnormality demonstrable by extensive studies which included cardiac catheterization. A brother of this patient, who probably suffers from a forme fruste, demonstrates inverted P waves bespeaking an ectopic pacemaker. The father, who had aortic regurgitation and died suddenly at the age of 28 years, had either ectopic pacemaker or prolongation of the P-R interval with superimposition of P waves on T waves.

**Pulmonocardiac Failure**

Very pronounced kyphoscoliosis occurs in some of these patients, due usually to laxity and redundancy of the spinal ligaments but occasionally to hemivertebra (figure 7). It is remarkable that in no case has this thoracic deformity been clearly the cause of even a portion of the cardiovascular dysfunction observed. Particularly is this surprising in light of the fact that these patients seem to be prone to repeated pulmonary infection which is certainly an important factor in the cor pulmonale of kyphoscoliosis.

**The Cardiac Effects of Pectus Excavatum**

Very severe pectus excavatum has been observed in some cases of Marfan's syndrome. The two types of chest deformity which may occur, pigeon breast and pectus excavatum, are apparently the result of excessive longitudinal growth of the ribs resulting in either projection or depression of the sternum.

Much has been written about cardiac disability resulting from pectus excavatum. Furthermore, since originally proposed by Flesch in 1873, excessive longitudinal growth of the ribs has been thought to
be the mechanism in many of the cases. The hereditary nature of the disorder has frequently been evident. Many of the patients with this chest deformity are described as unusually tall and thin with spinal curvature. In spite of these facts, it has not been appreciated that many of the patients with pectus excavatum are victims of a generalized disease which may have affected the cardiovascular system directly. In two surgical reports, there are three cases of pectus excavatum in which follow-ups has established the diagnosis of Marfan's disease. At least two other possible cases of Marfan's disease reported in the surgical literature as being instances of pectus excavatum with secondary cardiac effects are 1—the six-year-old patient described by Lester as having “systolic and diastolic murmurs and cardiac incompetence” and 2—the patient of Ravitch, a 23-year-old, 74-inch-tall man who had congestive heart failure and atrial fibrillation and who was specifically described by his physician as thin, gangly, loose-jointed and round-shouldered.

Without question simple pectus excavatum of severe grade can be accompanied by dyspnea, pain, and atrial dysrhythmias. It also can produce loud systolic murmurs. Whether it alone produces congestive heart failure in young individuals, requires careful re-examination of the patient and the medical status of other members of his family.

Although physical signs are difficult to interpret in the presence of pronounced thoracic deformity, a basilar diastolic murmur must be considered, in the light of our present knowledge, an indication of aortic involvement and a contraindication to surgery for sternal malformation. The Graham-Steell type of pulmonary diastolic murmur sometimes heard in kyphoscoliotic heart disease need not be a source of confusion.

In general, surgical repair of the pectus excavatum has been as successful in these cases as in those without the rest of Marfan's syndrome. Healing is not impaired, according to the observation of surgeons who repair the hernias, close cleft palates or remove ectopic lenses in these cases. (See ref. 32 for an exception.) However, it is recommended that correction of pectus excavatum in Marfan's syndrome be postponed until after puberty when rib growth has ceased.

The following case demonstrates two complications of Marfan's disease. Severe pectus excavatum was present and in the period following operation for repair of this deformity, fatal dissecting aneurysm of the aorta occurred. An aortic diastolic murmur had been present before operation. Like case W. W. above, dilatation of the ascending aorta almost certainly preceded the development of the dissecting aneurysms.

K. B.,* a 24 year old white man, was admitted to the Medical College of Virginia Hospital after a year of increasing dyspnea. Twenty-four days before admission he had suddenly become markedly dyspneic and had severe palpitation and substernal pain. About two weeks before admission he had a second episode of pain and palpitation. Following the first attack his dyspnea progressed more rapidly than before and he also became orthopneic.

Physical examination revealed a slender, underdeveloped, undernourished man who was dyspneic even at rest. There was pronounced pectus excavatum (figure 9). The heart was markedly displaced to the left with the point of maximum impulse in the midaxillary line and the seventh and eighth intercostal spaces. The left anterior chest wall heaved with each heart beat. There was a loud continuous machinery-like murmur over the base of the heart with a systolic thrill. Blood pressure was 90/40 in the right arm and 110/32 in the left.

On Nov. 5, 1949 surgical repair of the pectus excavatum was performed. The patient withstood the operation well and remained in a satisfactory condition until 48 hours later when he suddenly went into circulatory collapse and died in less than two hours after developing pronounced distension of the cervical veins.

At autopsy the body measured 72 inches in length. The arms and legs were very slender and long with poor muscular development. The left leg was shorter than the right and showed partial club foot. Bilaterally the first and second toes were unusually long but the fourth toes shorter than normal. There were flexion deformities of the fingers, deformed teeth with malocclusion, bifid uvula, and lumbar kyphosis.

The heart weighed 550 Gm. The increase in

* This patient is included through the courtesy of Drs. W. B. Porter and I. A. Bigger.
weight and size was the result of left ventricular hypertrophy and dilatation. The pericardial sac contained 880 cc. of blood. The ascending aorta and first portion of the arch were markedly dilated and in addition there was a dissecting aneurysm of the wall extending from an intimal tear about 3 cm. above the aortic ring to the point where there was slight coarctation of the aorta between the left subclavian and left common carotid ostia. Just distal to the left subclavian a second dissection began and extended throughout the rest of the aorta to involve the first portion of both iliac arteries. A small rent on the anterolateral surface of the ascending aorta represented the spot where perforation into the pericardial sac had occurred.

Histologically both dissections were endothelialized and showed some atheroma formation. In addition the media showed pronounced changes of the types described in other cases of aortic abnormality in this series, particularly L. K. above.

**Other Cardiovascular Abnormalities**

Except for one report47 of dilatation of the left external carotid artery (not studied anatomically), no evidence of abnormality in peripheral vessels has been discovered. Dissection may extend out from the aorta an appreciable distance into the peripheral arteries but these have been histologically normal.50 No pericardial peculiarity such as diverticulum or cyst, has been reported.

**Coexistent Cardiovascular Lesions**

*Rheumatic Fever.* It was suggested by Futcher and Southworth29 that patients with Marfan's disease may have more than average susceptibility to rheumatic fever. In addition to their case, at least three patients in this series had illnesses consistent with the diagnosis of rheumatic fever. Whether this represents an abnormally high incidence is difficult to state. Certainly the incidence is not striking. Furthermore, in no instance has an unmistakable rheumatic lesion such as mitral stenosis been found clinically or post mortem in a patient with arachnodactyly.

*Syphilis.* A reported case30 and at least four of my cases have had positive serological tests for syphilis. Two of these patients had severe aortic regurgitation with death after brief illnesses. Autopsy was unfortunately not performed. The combination of syphilis and Marfan's syndrome might be expected to have dire effects on the aorta. Congenital syphilis was present in a recently reported patient with aortic dilatation.58

*Hypertension.* Two of my patients appear to have essential hypertension. Although the aorta at their present ages of 27 and 25 years shows no abnormality clinically, the hypertension may place them in additional jeopardy from dissecting aneurysm and the other aortic complication of their connective tissue disorder. A patient with Marfan's disease and malignant hypertension has been described to me by Dr. Milton Landowne.

*Pregnancy.* There is suggestive evidence that dissecting aneurysm of the aorta occurs with increased incidence in pregnancy. (In one review31 of 49 cases of fatal dissecting aneurysm in females under the age of 40 years, about one-half were pregnant women.) The mechanism is unknown. A general loosening of connective tissues, apparently on a hormonal
basis, is striking in lower animals including monkeys. Some orthopedists have the impression that a similar loosening of articular structures occurs in human pregnancy. In spite of these theoretical considerations pregnancy has not been observed to have any ill effects on the patients we have followed. But the 23 year old patient with Marfan’s disease, reported by Lindeboom and Bouwer, was pregnant when she succumbed to dissecting aneurysm.⁵⁰

AN UNUSUALLY SEVERELY AFFECTED FAMILY

By way of summary, herewith the story of a family which was unusually heavily affected by the cardiovascular complications of Marfan’s syndrome. Figure 10 presents the pedigree of this family, affected probably through at least four generations. Individual I-1 died suddenly in 1897 at the age of 47 years, presumably of apoplexy. This may have been dissecting aneurysm. The son of this man (II-5) died at the age of 27 years after a very brief illness of undiagnosed nature. He was six feet tall, was always very thin and had been sent to Texas at one point for suspected tuberculosis. He became ill at noon one day and was dead at 5 a.m. the following day. He was said to have had no pain but developed hematuria in the late afternoon of the day he became ill.

Most of the remainder of the story of this family is told in the words of individual II-6, an intelligent observer and cooperative informant. Her husband (III-5) died in 1945 at the age of 32 years. “His heart condition was diagnosed as endocarditis by a heart specialist. He was apparently in good health up to two months prior to his death. He was 6 feet 2½ inches tall and in the last two years of his life he weighed more than ever before—175 pounds—and appeared to be in excellent health, except for his failing eyesight. He was working exceptionally hard due to the wartime manpower shortage. He was appointed to a job which necessitated a great deal of coast-to-coast flying at high altitudes. It was on one of these trips that he was taken ill. He returned home, was put to bed and given medicine to which he responded beautifully. He insisted on going on another trip and lived one month after his return. He was hospitalized but his case was pronounced hopeless. He had a hernia operation two years before his death. A routine check-up before the anesthesia showed no heart condition then.

The daughter of this man (IV-7) “was born May 17, 1937. She was always frail. She and her brother had whooping cough when they were six and five years old. Her heart started enlarging at that time. She was extremely nearsighted and wore glasses from the age of three years. She had a bad spinal curvature that we first noticed when she was ten. The family doctor did not advise a brace or cast as she was so frail and her heart was getting increasingly worse. During her last illness which lasted six weeks, the doctor said that her heart was just as it would have been in a person in his forties who had had rheumatic fever in his youth, that her heart was just worn out. She died at the age of 12½ years and was 5 feet 2 inches tall in spite of a very bad curvature. She had a brilliant mind and was at the top of classes in spite of her many handicaps. Both of the children were thin to the point of looking emaciated.”

The brother of this girl (IV-8) “was born Nov. 27, 1938. He and Catharine looked like twins and were as nearly like their father as was possible. He was well as a baby and up to the time that he had whooping cough at the age of five. After that long siege of coughing, the doctor discovered that he had a heart murmur. His heart enlarged so that his chest protruded. He complained of chest pain occasionally. He died suddenly in August 1946. His sister said after he died that he had complained of severe chest pains a couple of days before but he didn’t tell anyone else. He developed hernia when he was about two years old but it never seemed to bother him. He had a bad case of influenza the winter before he died and had a bad cough that lingered all winter and we felt hastened his death.”

At age 7 this patient was 53 inches tall and weighed 51 pounds. He showed arachnodactyly, hypotonia, hammer toes, thin and translucent skin, ectopia lentium, cardiomegaly, dilatation of the aorta, aortic systolic and diastolic murmurs, left axis deviation (by electrocardiogram), deformity (not described in detail) of the hip joints and skull (by x-ray examination). The lenses in this case were misplaced downward and outward.
GENERAL COMMENTS

It must be emphasized that the principal cardiovascular component of Marfan's syndrome, the abnormality of the aorta, is not in the true sense "congenital heart disease" or a "congenital malformation". It is comparable to the abiotrophies of the neurologists: the weakness is present at birth, although perhaps not recognizable by ordinary histologic technique, it expresses itself only later in extra-uterine life, often very late.

It has been suggested by several writers that many cases of so-called Erdheim's cystic medial necrosis with dissecting aneurysm are not apparent instances of Marfan's syndrome. Other factors than hypertension must certainly play a role in dissecting aneurysm since there is a significant proportion of occurrences in normotensive individuals. Furthermore, experience at this hospital and elsewhere is that 20 to 25 per cent of cases of dissecting aneurysm occur in persons under 40 years of age. Frei encountered this lesion in a 14 month old individual and in a boy of 10 years. Erdheim's cystic medial necrosis has been observed to produce diffuse aortic dilatation in a patient who was not noted to have the stigmata of Marfan's syndrome. It seems possible that the morphologic entity which Erdheim described may not be a homogeneous entity etiologically but may, in individual instances, have various pathogeneses, hereditary and acquired. One of these causes is the hereditary connective tissue defect of Marfan's syndrome. The connective tissue defect of Ehlers-Danlos syndrome may be a second hereditary cause (see below).

Although what element of connective tissue is primarily defective in Marfan's syndrome is unknown, there are some reasons to suspect that it is the elastic fiber or an element intimately related to the elastic fiber. From the end-stage findings in a case such as that illustrated by figure 5 a to d, it is difficult to reconstruct the chain of pathogenetic events. However, one seemingly plausible reconstruction interprets the disruption of the elastic lamellae as primary. Then the smooth muscle fibers which normally have their origin and insertion on the elastic plates collapse together and apparently undergo pronounced hypertrophy and hyperplasia, possibly as a compensatory mechanism. The increased vascularization of the aortic media may be a response to these changes in the smooth muscle.

The production in rats of a somewhat analogous, but acquired, syndrome has been of great interest for obvious reasons. Kyphoscoliosis, hemia and either dissecting, diffuse, or saccular aneurysm of the aorta are produced by the feeding of a toxic agent contained in the seed of Lathyris odoratus. Although there are reasons to believe that the basic defects are not identical in these two syndromes, experimental studies such as this may provide a lead on the inborn metabolic aberrations which are the basis of the morphologic abnormality of the aorta in Marfan's syndrome and on the acquired aberration in the case of "metabolic" dissecting aneurysm such as that which may occur during pregnancy and with hypothyroidism.

My data indicate that approximately 15 per cent of all cases occur as a result of de novo mutation. In the remaining instances, the victim was a descendant of such an original case or descended in a line with Marfan's syndrome present in each generation as far back as it was possible to trace. Once having occurred by mutation in a family line, the Marfan trait is inherited as a dominant.

About 80 per cent of the cases have ectopia lentis. When ectopia lentis was absent it was frequently difficult to be certain about the diagnosis of Marfan's disease. On the other hand, the other stigmata of Marfan's syndrome may be so subtle that for practical purposes it is probably safer to consider all cases of ectopia lentis potential victims of the aortic complications here discussed. This is assuming, of course, that the ectopia lentis is not clearly part of some other syndrome such as that of Weill and Marchesan in which the victim shows striking brachymorphism rather than the dolichomorphism of Marfan's syndrome (fig. 11).

In the differential diagnosis of Marfan's
VICTOR A. McKUSICK

FIG. 11 A

FIG. 11 B

Fig. 11 A and B. Shown here are father and daughter with the Weill-Marchesani syndrome (ectopia lentis and brachymorphism). The skeletal manifestations are the antithesis of those of Marfan’s syndrome. The daughter has a cleft palate and is mentally defective. No definite cardiovascular abnormality has been identified in cases of this syndrome. Compare these father-daughter pictures with that in figure 3 A.

disease the malformations resulting from Rh incompatibility and from maternal rubella are important. Mother-child blood typing and the history may aid in the differential. Given a case with skeletal proportions consistent with Marfan’s disease and a complication, such as aortic regurgitation, which might be on that basis, it is virtually impossible to be completely certain whether Marfan’s disease is actually present unless 1—ectopia lentis, the least equivocal component of the syndrome, is also present or 2—unequivocal instances of the syndrome are represented by other members of the family. In the Negro, in particular, a habitus confusingly suggestive of Marfan’s syndrome is frequently met. Some of these are a forme fruste of the syndrome; most of them are merely anthropologic variants. (For example, one famous contemporary Negro basketball star has a height of 75½ inches and an arm span of 84 to 86 inches.) Eunuchism and sickle cell disease are two pathologic conditions which are accompanied by skeletal changes like those of Marfan’s disease.

Currently under study are two other hereditary disorders of connective tissue in which cardiovascular involvement occurs. One, pseudoxanthoma elasticum, is clearly a systemic dystrophy, probably of collagen than elastic fibers, with important generalized arterial involvement. In the other condition, Ehlers-Danlos syndrome (hyperelastica cutis), the evidence of cardiovascular involvement is much less conclusive although associated congenital malformations of the heart, specifically interatrial septal defect and tetralogy of Fallot, have been reported in individual patients with this last syndrome. I have encountered one patient with Ehlers-Danlos syndrome who succumbed to dissecting
aneurysm of the aorta. In this patient, a 27 year old white man, dissection began in the renal artery producing retroperitoneal hematoma and leading to laparotomy.

**Summario in Interlingua**

Del puncto de vista clinic le morbo de Marfan se presenta como un abiotrophia de alicum elemento del textos conjunctive. Su manifestationes cardiovascular resulta de defective medios aortic, de defective cuspides valvular, de communicationes interatral, e de pectore excavate. Le defecto del medios aortic se manifesta per aneurysma dissecente, per aneurysma diffuse del aorta ascendente, e per un combination de ambas. Nos presenta un description de subacute endocarditis bacterial in un paciente con morbo de Marfan. Defectos del septo interatral es minus frequente que previemente suponite. Symptomas cardiac in sever casos de pectore excavate debe esser evalutate in consideration del possibile presentia de morbo de Marfan. Nos ha colligite datos ab cinquanta familias in qui occurrava al minus un caso indubitabile de morbo de Marfan.

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